REMARKS

Claims 57 – 68 are pending, with claim 68 having been withdrawn from consideration pursuant to a prior election of species.

Amendments to the claims

Claim 57, the sole independent claim, is being canceled in favor of two new independent claims, claims 69 and 70, which are respectively drawn to the elected (claim 69) and the non-elected (claim 70) species of "Parkinson disease agent" to be administered concurrently with safinamide; claim 70, drawn to the nonelected species, is marked as "new-withdrawn." Claim 58 is being canceled as redundant over new claim 69 and claim 68 is being canceled as redundant over new claim 70. Claim 67 is canceled for clarity. Consequential amendments to revise dependencies are being made to claims 59 – 65, which now depend from new independent claim 69. Claim 64 is additionally amended to recite "levodopa" instead of "L-DOPA"; the terms are synonymous, with "levodopa" being the official international nonproprietary name.

Accordingly, after entry of the amendments presented herein, claims 59 – 66 and 69 – 70 are pending, with new claim 70 standing withdrawn as drawn to the previously nonelected species.

Rejections under 35 U.S.C. § 103

Claims 57 – 64 stand rejected under 35 U.S.C. § 103(a) as having been obvious over Dostert *et al.*, U.S. Pat. No. 5,236,957 ("Dostert") and Chiesi, U.S. Pat. No. 5,017,607 ("Chiesi"). Claims 65 and 66 stand rejected under 35 U.S.C. § 103(a) over Dostert and Chiesi, further in view of Chenard *et al.*, U.S. Pat. No. 6,258,827 ("Chenard").

Applicants maintain their traversal of these rejections for the reasons elaborated in the response filed June 15, 2010, further in view of the Third Declaration of C. Warren Olanow ("3rd Olanow Dec.") filed herewith. Given the advanced state of the safinamide clinical trial program[1], however, applicants have canceled claim 57 in favor of new independent claim 69,

[1] *See* 3rd Olanow Dec., ¶¶ 5 *et seq.*

formally obviating the rejections, in order to expedite prosecution. For the reasons advanced below, the rejections would be in error if renewed against the claims now pending. Accordingly, the rejections should be withdrawn.

The Office correctly characterizes Dostert as teaching the use of safinamide in treatment of Parkinson's disease, also correctly noting that "Dostert does not teach the coadministration of L-Dopa[2] ... in an amount that alone has therapeutic effect," Final Office Action at pp. 4 – 5 (quoting from then-pending claim 57, now canceled).[3] Chiesi, which does not mention safinamide, is cited as teaching the administration of L-dopa methyl ester (LDME), a levodopa prodrug, "advantageously ... in combination with other active principles, selected from peripheral decarboxylase inhibitors, such as carbidopa or benserazide, or selective MAO-B inhibitors, such as Deprenyl," Final Office Action at page 5. Arguing that "there is no indication [in Chiesi] that the dosage of LDME alone would not be therapeutically effective," Final Office Action at p. 3,[4] the Examiner argues that "[i]t would have been obvious to one of ordinary skill in the art at the time of the invention to have combined safinamide, used to treat Parkinson's disease, as taught by Dostert, with a combination of L-dopa methyl ester and peripheral decarboxylase inhibitor, as taught by Chiesi, for the same purpose." Final Office Action at p. 5.

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2 Synonymously, "levodopa."

3 Claim 57, now canceled, recited as follows:

> 57. A method of treating idiopathic Parkinson's disease, comprising:
> orally administering safinamide, or a pharmaceutically acceptable salt thereof, on a daily dosage schedule of about 0.5 mg/kg/day to about 5 mg/kg/day to a patient with idiopathic Parkinson's disease; and
> concurrently administering to the patient at least one Parkinson's disease agent, wherein the at least one Parkinson's disease agent is selected from the group consisting of L-Dopa and Dopamine agonists, and ***wherein the at least one Parkinson's disease agent is administered in an amount that alone has therapeutic effect***. (emphasis added)

4 In light of the amendments made herein, applicants will not belabor the point that the Office's reliance on such allegedly inherent disclosure, rather than on express teachings in the prior art reference, is impermissible in the context of obviousness. *In re Spormann*, 150 USPQ 449, 452 (CCPA 1966); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 220 USPQ 303, 314 (Fed. Cir. 1983); *In re Dillon*, 16 USPQ2d 1897, 1922 (Fed. Cir. 1990) (*en banc*).

Claim 57 has now been canceled in favor of new claim 69, which no longer recites that levodopa is "administered in an amount that alone has therapeutic effect." Instead, drafted in Jepson format, claim 69 recites as follows:

> 69 (new). In a method of treating idiopathic Parkinson's disease in a patient receiving a stable dose of levodopa, the improvement comprising:
> concurrently administering safinamide, or a pharmaceutically acceptable salt thereof, on an oral dosage schedule of about 0.5 mg/kg/day to about 5 mg/kg/day,
> without reducing the patient's dose of concurrently administered levodopa.

Whether or not the LDME doses that are disclosed in Chiesi – either expressly or inherently – would alone have exerted a therapeutic effect, it is manifestly clear that Chiesi neither teaches nor suggests that the dosage of levodopa or LDME be maintained without reduction when further agents are added to the treatment regimen. To the contrary, Chiesi specifically teaches that the addition of an MAO-B inhibitor to therapy with levodopa methyl ester "allow[s] a **remarkable reduction in the dose of LDME** necessary to control the disease, consequently decreasing side effects...." Chiesi, col. 3, lines 9 – 16 (emphasis added).[5] Safinamide is a potent inhibitor of MAO-B. Dostert, col. 11, lines 33 – 42. Read in conjunction with Dostert, Chiesi is thus properly understood to **teach away** from the addition of safinamide to the treatment regimen of a "patient receiving a stable dose of levodopa," "**without reducing the patient's dose of concurrently administered levodopa**," as now claimed.

This alone is sufficient to defeat any *prima facie* case of obviousness based on the Chiesi reference.[6] The PTO bears the initial burden of presenting a *prima facie* case of obviousness. When the PTO fails to meet its burden, applicants are entitled, without more, to issuance of the patent. *In re Glaug*, 62 USPQ2d 1151, 1152 (Fed. Cir. 2002) (reversing the Board's holding of

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[5] That MAO-B inhibitors permit remarkable reductions in levodopa dosage is not a remarkable observation, nor original to Chiesi: inhibition of central catabolic pathways has long been known to permit effective concentrations of levodopa (and thus, of dopamine) to be achieved in brain using lower administered dosages of levodopa; indeed, a primary purpose of adjunctive administration of MAO-B inhibitors is to permit just such dosage reduction. *See* 3rd Olanow Dec., ¶¶ 16-18.

[6] "A *prima facie* case of obviousness may ... be rebutted by showing that the art, in any material respect, teaches away from the claimed invention...." M.P.E.P. § 2144.05III (8th ed., rev. 6).

obviousness for failure to state an adequate *prima facie* case); *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992) ("If examination at the initial stage does not produce a *prima facie* case of unpatentability, then without more the applicant is entitled to grant of the patent."); *In re Grabiak*, 226 USPQ 870, 873 (Fed. Cir. 1985) ("On the record before us, we conclude that the PTO did not establish a *prima facie* case of obviousness, and thus did not shift to Grabiak the burden of coming forward with evidence of unexpected results.").

Nonetheless, in order to expedite allowance, and without thereby admitting to the sufficiency of the *prima facie* case, applicants submit herewith the Third Declaration of Dr. C. Warren Olanow under 37 C.F.R. § 1.132 ("3rd Olanow Dec."). As summarized briefly below and elaborated at greater length in the Declaration and its attached exhibits, the addition of safinamide to a stable dose of levodopa, without reduction in concurrent levodopa dosage, provides unexpected, and unexpectedly superior, clinical results, satisfying a long-felt, but as yet unmet, therapeutic need, objective *indicia* of nonobviousness that suffice to rebut any purported *prima facie* case of obviousness.

Briefly, "certain basic principles ... inform and guide current therapy" of Parkinson's disease:

> **A.** Four decades after its introduction, levodopa remains the most effective treatment for Parkinson's disease and the "gold standard" against which other therapies must be compared. Indeed, no medical or surgical therapy that is currently available has been demonstrated to provide antiparkinsonian benefits that are superior to that which can be achieved with levodopa.
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> **B.** However, chronic levodopa treatment is associated with side effects, known as motor complications: motor fluctuations, such as "wearing off," which constitutes a loss of the motor benefit prior to the ensuing dose, and involuntary movements, known as dyskinesia. These levodopa-induced motor complications may be mild in the early stages of the illness, but can become severe and disabling to PD [Parkinson's disease] patients in the more advanced stages. The cause of levodopa-induced motor complications is not precisely known, but is directly related to the

levodopa dose – in particular, higher doses of levodopa are associated with an increased risk and increased frequency of dyskinesia.

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C. As a consequence, the treating physician is presented with a dilemma, and frequently cannot provide patients with optimal treatment. In the early stages, the levodopa dosage can be titrated in an attempt to achieve an acceptable compromise between motoric benefit, on the one hand, and dyskinesia, on the other. In later stages, however, patients may experience disability no matter how levodopa is administered. As a compromise, physicians often administer levodopa in dosages that provide suboptimal motor benefit in order to minimize the risk of dyskinesia. Thus PD patients in the modern era are often undertreated in order to prevent the development of potentially disabling dyskinesia.

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D. The inability to administer levodopa at doses that provide optimal motoric benefit presents a longstanding, and unsolved, clinical need.

3rd Olanow Dec., ¶ 3.

"Safinamide has the potential to satisfy this unmet need. As detailed below, phase III clinical trials have demonstrated that safinamide ***increases the motoric benefit*** of concomitantly administered stable and optimal doses of levodopa without ***increasing, and potentially decreasing, the risk and severity of dyskinesia***." 3rd Olanow Dec., ¶ 4 (emphasis in the original).

"The 016 Study was a prospective, randomized, placebo-controlled, double-blind 6 month (24 week) study conducted in multiple centers throughout the world.... Patients recruited into the study had idiopathic Parkinson's disease of greater than three years' duration, were being treated with stable and optimized doses of levodopa, and were experiencing motor fluctuations with > 1.5 hours of 'OFF' time per day. Prior to entry into the study, efforts were made to titrate the dose of levodopa so as to maximize clinical benefit and minimize 'OFF' time and dyskinesia. Patients were then randomly assigned to one of three treatment arms: (i) addition of placebo, (ii) addition of 50 mg/day safinamide, or (iii) addition of 100 mg/day

safinamide. **In each of the groups, the optimized and stable dose of levodopa was maintained for the duration of the study**...." 3rd Olanow Dec., ¶ 6 (emphasis added).

"The results showed that the addition of both 50 mg/day and 100 mg/day of safinamide to stable and optimized doses of levodopa resulted in a statistically significant and dose-related improvement in motor function, measured as a decrease in Part III of the Unified Parkinson's Disease Rating Scale ('UPDRS Part III'), which is a composite measure of motor function...." 3rd Olanow Dec., ¶ 7. "This improvement in motor function was accompanied by a significant increase in "ON" time (periods in which Parkinson motor features are well controlled) at both doses of safinamide." 3rd Olanow Dec., ¶ 7 "Critically, this improvement in motor function and in "ON" time was achieved without any increase in dyskinesia, as assessed by both the Unified Parkinson's Disease Rating Scale ("UPDRS") and the Dyskinesia Rating Scale ("DRS")." 3rd Olanow Dec., ¶ 7 (original emphasis omitted).

"Study 018 was a double-blind, placebo-controlled extension of the 016 study in which patients who had completed the 6-month (24 week) trial were then continued for an additional 18 months in the same treatment arm to which they had initially been randomized. The improvement in 'ON' time observed with both doses of safinamide at 6 months in the 016 study was maintained over the course of the additional 18 months of follow up. Again the benefits achieved with safinamide were dose-related...." 3rd Olanow Dec., ¶ 8.

"I am not aware of any medical therapy that has been demonstrated to provide such a sustained motor benefit (increased 'ON' time) in a double blind trial of this duration." 3rd Olanow Dec., ¶ 8. "Furthermore, this sustained improvement in motor function **was not accompanied by any increase in dyskinesia**, as measured using the dyskinesia rating scale ('DRS'). Indeed, there was a trend, observed at both doses of safinamide, **to reduce the dyskinesia severity** in a dose-related fashion, even as the drug simultaneously improved motor function...." 3rd Olanow Dec., ¶ 8 (emphasis in the original).

In summary, "[t]he 016 and 018 Studies demonstrate that safinamide provides sustained anti-parkinsonian motor benefit when added to stable and optimized doses of concurrently administered levodopa, without causing a concomitant increase in, and indeed tending to reduce,

dyskinesia. If safinamide is approved by FDA, these properties would help to address a long-sought, unmet, critical need in the management of P[arkinson's] D[isease]." 3rd Olanow Dec., ¶ 9.

Although levodopa dosages differed among patients in the 016 and 018 studies, 3rd Olanow Dec., ¶ 11, and although "most of the patients enrolled in Study 016 (and who thus continued into Study 018) were also being treated with standard anti-parkinsonian agents in addition to levodopa," 3rd Olanow Dec. ¶ 12, "the inclusion criteria used for the 016/018 study were appropriate and in keeping with the standard for clinical trials in patients with Parkinson's disease," 3rd Olanow Dec. ¶ 14.

"Safinamide's ability to improve motoric benefit when added to optimized stable doses of levodopa, without increasing (and perhaps decreasing) dyskinesia, was unexpected, and could not have been predicted from safinamide's known ability to inhibit monoamine oxidase-B (MAO-B)." 3rd Olanow Dec., ¶ 15.

"MAO-B inhibitors have long been used in treatment of Parkinson's disease. By blocking catabolism of dopamine in the brain, MAO-B inhibitors raise striatal dopamine concentrations; increased dopamine concentrations at the site of the primary neuronal defect in the striatum improves motor symptoms in Parkinson's disease. Safinamide has long been known to inhibit MAO-B, and was on that basis previously predicted to be therapeutically effective in treating Parkinson's disease."[7] 3rd Olanow Dec., ¶ 16.

"However, the increase in dopamine levels occasioned by MAO-B inhibition is well-known **to increase** the frequency and severity of dyskinesia – this should come as no surprise, since the end-result of inhibiting the MAO-B enzyme, increased dopaminergic tone, is effectively the same as the end-result of increasing the dose of levodopa, which is metabolically converted to dopamine…." 3rd Olanow Dec., ¶ 17 (emphasis in the original). "Safinamide's ability to increase the motor benefit of concurrently administered levodopa **without increasing**

[7] See Dostert *et al.*, U.S. Pat. No. 5,502,079 (of record).

(and indeed, possibly *decreasing*) dyskinesia – and thus, the ability to add safinamide to an optimized levodopa treatment regimen without having to reduce levodopa dosage (*i.e.*, to a stable dose of levodopa) – would not have been predicted from its known ability to inhibit the monoamine oxidase-B (MAO-B) enzyme." 3rd Olanow Dec., ¶ 18 (emphasis in the original).

Dr. Olanow concludes that "[b]ased on all of the above, it is my opinion that safinamide is a unique molecule that offers the potential for unique treatment effects in PD. It has been demonstrated to provide anti-parkinsonian benefits to patients receiving optimized and stable doses of levodopa, and does so without increasing dyskinesia, even showing a trend towards reduction of dyskinesia. There is also a suggestion that safinamide might provide benefits with respect to mood and cognition. This combination of benefits … has not been demonstrated with any other antiparkinsonian therapy, was unexpected, and would satisfy a well-documented, longstanding, unmet medical need." 3rd Olanow Dec., ¶ 20.

Applicants commend the Examiner's attention to the supporting details and further explanation set forth at length in Dr. Olanow's Declaration and its attached exhibits. The evidence is compelling, the rejection should be withdrawn, and applicants' claims, as amended herein, passed to issue.

CONCLUSION

Claims 59 – 66 and 69 – 70 are pending, with new claim 70 standing withdrawn as drawn to the previously nonelected species. The rejections remaining in this application have been obviated by amendment, and fully traversed. The rejections should be withdrawn, and applicants' claims allowed.

Request for Telephonic Interview

Applicants and the undersigned attorney of record again thank the Examiner and her Supervisor for the courtesy extended in prior interviews, and request that if any additional

questions remain before allowing the instant claims, the Examiner call the undersigned attorney of record for a telephonic interview.

Fees

No fees beyond those specified in the accompanying fee transmittal are believed to be due in connection with this response. However, the Director is authorized to charge any additional fees that may required, or credit any overpayment, to Dechert LLP Deposit Account No. 50-2778 (**Order No. 373987-011 US (102895)**).

Respectfully submitted,

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